CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 040234

Trade Name: OXYCODONE AND ACETAMINOPHEN CAPSULE USP 5MG/500MG

Generic Name: Oxycodone and Acetaminophen Capsule USP 5mg/500mg

Sponsor : Royce Laboratories, Inc.

Approval Date: October 30, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 040234

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Pharmacology Review(s)				
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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 040234

APPROVAL LETTER

ANDA 40-234

OCT 30 1997

Royce Laboratories, Inc.
Attention: William Stahovec
16600 NW 54 Avenue
Miami, FL 33014

Dear Sir:

This is in reference to your abbreviated new drug application dated December 20, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Oxycodone and Acetaminophen Capsules USP, 5 mg/500 mg.

Reference is also made to your amendments dated July 28, and August 22, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Oxycodone and Acetaminophen Capsules USP, 5 mg/500 mg, to be bioequivalent and, therefore, therapeutically equivalent to those of the listed drug (Tylox® Capsules, 5 mg/500 mg, of RW Johnson Pharmaceutical Research Institute).

Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising,

and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/ 10/30/97

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040234

FINAL PRINTED LABELING

Each capsule contains:
Oxycodone hydrochloride, USP ..... 5 mg*
Acetaminophen, USP ..... 500 mg
*5 mg oxycodone HCl is equivalent to 4.4815 mg of oxycodone

Usual Adult Dosage:
One capsule every six hours as needed
For dosage and other prescribing information see accompanying product literature.
Store at controlled room temperature, 15°-30°C (59°-86°F).
Protect from moisture.
Dispense in a tight, light-resistant container as defined by the USP.
DEA ORDER FORM REQUIRED

Royce™ NDC 51875-0406-1

OCT 30 1997

OXYCODONE* AND ACETAMINOPHEN CAPSULES, USP

C II

5 mg*/500 mg

***WARNING:** May be habit forming

CAUTION: Federal law prohibits dispensing without prescription.

APPROVED

100 Capsules

Mfd. By: Royce Laboratories, Inc., Miami, FL 33014

Batch No.:

Exp. Date:

N 3 51875-0406-1 6

Each capsule contains:
Oxycodone hydrochloride, USP ..... 5 mg*
Acetaminophen, USP ..... 500 mg
*5 mg oxycodone HCl is equivalent to 4.4815 mg of oxycodone

Usual Adult Dosage:
One capsule every six hours as needed
For dosage and other prescribing information see accompanying product literature.
Store at controlled room temperature, 15°-30°C (59°-86°F).
Protect from moisture.
Dispense in a tight, light-resistant container as defined by the USP.
DEA ORDER FORM REQUIRED

Royce™ NDC 51875-0406-2

OCT 30 1997

OXYCODONE* AND ACETAMINOPHEN CAPSULES, USP

C II

5 mg*/500 mg

***WARNING:** May be habit forming

CAUTION: Federal law prohibits dispensing without prescription.

APPROVED

500 Capsules

Mfd. By: Royce Laboratories, Inc., Miami, FL 33014

Batch No.:

Exp. Date:

N 3 51875-0406-2 3

Each capsule contains:
Oxycodone hydrochloride, USP ..... 5 mg*
Acetaminophen, USP ..... 500 mg
*5 mg oxycodone HCl is equivalent to 4.4815 mg of oxycodone

Usual Adult Dosage:
One capsule every six hours as needed
For dosage and other prescribing information see accompanying product literature.
Store at controlled room temperature, 15°-30°C (59°-86°F).
Protect from moisture.
Dispense in a tight, light-resistant container as defined by the USP.
DEA ORDER FORM REQUIRED

Royce™ NDC 51875-0406-4

OXYCODONE* AND ACETAMINOPHEN CAPSULES, USP

C II

5 mg*/500 mg

***WARNING:** May be habit forming

CAUTION: Federal law prohibits dispensing without prescription.

APPROVED

1000 Capsules

Mfd. By: Royce Laboratories, Inc., Miami, FL 33014

Batch No.:

Exp. Date:

N 3 51875-0406-4 7

OXYCODONE* AND ACETAMINOPHEN CAPSULES, USP C II

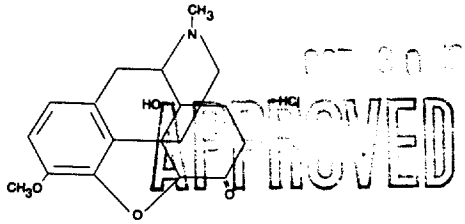
DESCRIPTION

Each capsule, for oral administration, contains:

Oxycodone hydrochloride, USP (equivalent to 4.4815 mg of oxycodone)	5mg
* **WARNING: May be habit forming**	
Acetaminophen, USP	500mg

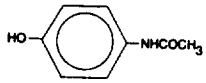
In addition, each capsule also contains the following inactive ingredients: black iron oxide, corn starch, D&C Yellow #10 aluminum lake, FD&C Blue #1 aluminum lake, FD&C Blue #1, FD&C Blue #2 aluminum lake, FD&C Red #40, FD&C Red #40 aluminum lake, gelatin, magnesium stearate, pharmaceutical glaze, povidone, pregelatinized starch, propylene glycol, and titanium dioxide.

The oxycodone component is 14-hydroxydihydrocodeinone, a white, odorless, crystalline powder having a saline, bitter taste. It is derived from the opium alkaloid thebaine, and may be represented by the following structural formula:



$C_{18}H_{21}NO_4 \cdot HCl$ Molecular Weight = 351.83

Acetaminophen, 4'-hydroxyacetanilide, is a non-opiate, non-salicylate analgesic and antipyretic which occurs as a white, odorless, crystalline powder with a slightly bitter taste. It may be represented by the following structural formula:



$C_8H_9NO_2$ Molecular Weight = 151.17

CLINICAL PHARMACOLOGY

The principal ingredient, oxycodone, is a semisynthetic narcotic analgesic with multiple actions qualitatively similar to those of morphine; the most prominent of these involve the central nervous system and organs composed of smooth muscle. The principal actions of therapeutic value of the oxycodone in this product are analgesia and sedation.

Oxycodone is similar to codeine and methadone in that it retains at least one-half of its analgesic activity when administered orally.

Acetaminophen is a non-opiate, non-salicylate analgesic and antipyretic.

INDICATIONS AND USAGE

Oxycodone and acetaminophen capsules are indicated for the relief of moderate to moderately severe pain.

CONTRAINDICATIONS

Oxycodone and acetaminophen capsules should not be administered to patients who are hypersensitive to oxycodone or acetaminophen.

WARNINGS

Drug Dependence: Oxycodone can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of oxycodone and acetaminophen capsules and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications. Like other narcotic-containing medications, oxycodone and acetaminophen capsules are subject to the Federal Controlled Substances Act (Schedule II).

PRECAUTIONS

General

Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute Abdominal Conditions: The administration of products containing oxycodone or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Special Risk Patients: Oxycodone and acetaminophen should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

Information for Patients

Oxycodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using oxycodone and acetaminophen capsules should be cautioned accordingly.

Drug Interactions

Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with oxycodone and acetaminophen may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

The concurrent use of anticholinergics with narcotics may produce paralytic ileus.

Pregnancy

Teratogenic Effects: Pregnancy Category C: Animal reproductive studies have not been conducted with oxycodone and

acetaminophen. It is also not known whether oxycodone and acetaminophen can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Oxycodone and acetaminophen should not be given to a pregnant woman unless in the judgment of the physician, the potential benefits outweigh the possible hazards.

Nonteratogenic Effects: Use of narcotics during pregnancy may produce physical dependence in the neonate.

Labor and Delivery: As with all narcotics, administration of oxycodone and acetaminophen to the mother shortly before delivery may result in some degree of respiratory depression in the newborn and the mother, especially if higher doses are used.

Nursing Mothers

It is not known whether oxycodone and acetaminophen are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when oxycodone and acetaminophen are administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

The most frequently observed adverse reactions include lightheadedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include euphoria, dysphoria, constipation, skin rash and pruritus. At higher doses, oxycodone has most of the disadvantages of morphine including respiratory depression.

DRUG ABUSE AND DEPENDENCE

Oxycodone and acetaminophen capsules are a Schedule II controlled substance.

Oxycodone can produce drug dependence and has the potential for being abused. (See **WARNINGS**).

OVERDOSAGE

Acetaminophen

Signs and Symptoms: In acute acetaminophen overdosage, dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma and thrombocytopenia may also occur.

In adults, hepatic toxicity has rarely been reported with acute overdoses of less than 10 grams and fatalities with less than 15 grams. Importantly, young children seem to be more resistant than adults to the hepatotoxic effect of an acetaminophen overdose. Despite this, the measures outlined below should be initiated in any adult or child suspected of having ingested an acetaminophen overdose.

Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

Treatment: The stomach should be emptied promptly by lavage or by induction of emesis with syrup of Ipecac. Patients' estimates of the quantity of a drug ingested are notoriously unreliable. Therefore, if an acetaminophen overdose is suspected, a serum acetaminophen assay should be obtained as early as possible, but no sooner than four hours following ingestion. Liver function studies should be obtained initially and repeated at 24-hour intervals.

The antidote, N-acetylcysteine, should be administered as early as possible, preferably within 16 hours of the overdose ingestion for optimal results, but in any case, within 24 hours. Following recovery, there are no residual, structural, or functional hepatic abnormalities.

Oxycodone

Signs and Symptoms: Serious overdosage with oxycodone is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur.

Treatment: Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The narcotic antagonist naloxone hydrochloride is a specific antidote against respiratory depression which may result from overdosage or unusual sensitivity to narcotics, including oxycodone. Therefore, an appropriate dose of naloxone hydrochloride (usual initial adult dose 0.4 mg to 2 mg) should be administered preferably by the intravenous route, and simultaneously with efforts at respiratory resuscitation (see package insert). Since the duration of action of oxycodone may exceed that of the antagonist, the patient should be kept under continued surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration.

An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression. Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated.

Gastric emptying may be useful in removing unabsorbed drug.

DOSAGE AND ADMINISTRATION

Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of narcotics. Oxycodone and acetaminophen capsules are given orally. The usual adult dosage is one capsule every 6 hours as needed for pain.

HOW SUPPLIED

Oxycodone and acetaminophen capsules USP (5mg oxycodone hydrochloride and 500 mg acetaminophen) are opaque white and opaque red hard gelatin capsules, filled with white powder. Cap imprinted with Royce Logo and body imprinted "5" over "500".

SIZE	ROYCE NDC NUMBER
Bottles of 100	51875-0406-1
Bottles of 500	51875-0406-2
Bottles of 1000	51875-0406-4

Store at controlled room temperature 15°-30° C (59°-86° F). Protect from moisture.

Dispense in a tight, light-resistant container as defined by the USP.

DEA Order Form Required.

Caution - Federal law prohibits dispensing without prescription.

Royce Laboratories, Inc.
16600 NW 54th Avenue
Miami, FL 33014

Revised: July 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040234

CHEMISTRY REVIEW(S)

ANDA 40-234

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 40-234

3. NAME AND ADDRESS OF APPLICANT
Royce Laboratories, Inc.
16600 NW 54 Avenue
Miami, FL 33014

4. LEGAL BASIS FOR SUBMISSION
The listed drug is Tylox® (Oxycodone and Acetaminophen Capsules USP), 5 mg/500 mg, NDA N88-790. Certification is included from Royce Laboratories that there are no unexpired patents and that the listed drug is not entitled to any period of marketing exclusivity.

5. SUPPLEMENT(s): N/A

6. PROPRIETARY NAME: N/A

7. NONPROPRIETARY NAME:
Oxycodone and Acetaminophen Capsules USP

8. SUPPLEMENT(s) PROVIDE FOR: N/A

9. AMENDMENTS AND OTHER DATES:
Firm:
Submitted: December 20, 1996
Facsimile amendment: July 28, 1997 (Subject of this review)

FDA:
Acknowledgment: February 24, 1997
Bio Letter: May 7, 1997
Letter, C.R. # 1: July 17, 1997

10. PHARMACOLOGICAL CATEGORY
Narcotic analgesic

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

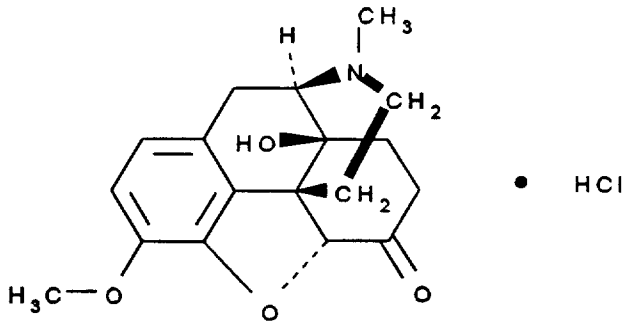
(b)4 - Confidential Business

13. DOSAGE FORM
Hard gelatin capsule

14. POTENCY
Oxycodone HCl: 5 mg
Acetaminophen: 500 mg

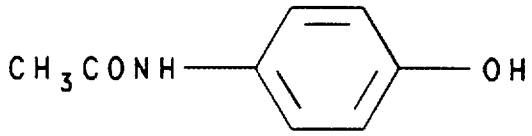
15. CHEMICAL NAME AND STRUCTURE

Oxycodone Hydrochloride
$C_{18}H_{21}NO_4.HCl$; M.W. = 351.83



4,5α-Epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride. CAS [124-90-3]

Acetaminophen USP
$C_8H_9NO_2$; M.W. = 151.16



Acetaminophen $C_8H_9NO_2$

4' Hydroxyacetanilide. CAS [103-90-2]

16. RECORDS AND REPORTS: N/A

17. COMMENTS

a. CMC issues satisfactory
b. Label review satisfactory - 9/4/97.
c. Bio satisfactory - 5/7/97.
d. Methods validation not required - USP items. Method verification satisfactory 6/20/97.
e. EIR acceptable for all firms 7/2/97.

18. CONCLUSIONS AND RECOMMENDATIONS

This ANDA can be approved.

19. REVIEWER: Donald Shostak

DATE COMPLETED: August 8, 1997
(Revised 9/8/97 - labeling)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040234

BIOEQUIVALENCE REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

ANDA 40-234

Food and Drug Administration
Rockville MD 20857

MAY 7 1997

Royce Laboratories, Inc.
Attention: Loren Gelber
16600 NW 54th Avenue
Miami. FL 33014

Dear Madam:

Reference is made to your abbreviated new drug application submitted December 20, 1996, pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Oxycodone and Acetaminophen Capsules USP.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

for Nicholas Fleischer, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

MAY - 6 1997

Acetaminophen and Oxycodone HCl Capsule. 500 mg/5 mg
ANDA # 40-234
Reviewer: Lin-Whei Chuang

Royce Laboratories, Inc.
Miami, FL
Submission Date:
December 20, 1996

Review of a Waiver Request

Oxycodone is a semisynthetic narcotic analgesic with multiple actions qualitatively similar to those of morphine. Its principal actions of therapeutic value in the drug product are analgesia and sedation. Acetaminophen is a non-opiate, non-salicylate analgesic and antipyretic.

The reference listed drug product is Tylox capsule (acetaminophen/oxycodone HCl, 500 mg/5 mg) manufactured by McNeil Laboratories/RW Johnson Pharmaceutical and approved under NDA #88790 on 12/12/84.

The firm requests a waiver from the human *in vivo* bioequivalence testing requirements because acetaminophen/oxycodone HCl capsule, 500 mg/5 mg, is rated AA in *Approved Drug Products with Therapeutic Equivalence Evaluation*, and the comparative dissolution testing data of the test and reference drug products conducted by the firm are presented below:

In Vitro Dissolution Testing

Drug (Generic Name): Acetaminophen/Oxycodone HCl
Dose Strength (form): 500 mg/5 mg (capsule)
ANDA No.: 40-234
Firm: Royce Laboratories, Inc.

I. Conditions for Dissolution Testing:

USP XXIII Apparatus: Paddle RPM: 50
No. Units Tested: 12
Medium: 0.1 N Hydrochloric Acid Volume: 900 ml
Tolerance: NLT [redacted](b)4) of both ingredients in 45 minutes
Reference Drug: Tylox Capsule (McNeil/RW Johnson)
Assay Methodology: [redacted](b)4 -

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # NC-1302 Strength (mg): 500/5 Amount of Acetaminophen Dissolved			Reference Product Lot # MP6501P Strength (mg): 500/5 Amount of Acetaminophen Dissolved		
	Mean %	Range	%CV	Mean %	Range	%CV
15	86.4	[redacted](b)4 -	7.7	80.2	[redacted](b)4 -	11.6

30	98.8	(b)4 - Confidential Business	3.6	96.8	(b)4 - Confidential Business	8.1
45	103.2		2.4	103.3		2.9
60	104.8		2.2	105.6		1.7
	Amount of Oxycodone Dissolved			Amount of Oxycodone Dissolved		
15	93.8	(b)4 - Confidential Business	7.8	85.1	(b)4 - Confidential Business	9.0
30	102.0		3.7	103.8		8.2
45	103.7		3.0	103.0		2.4
60	103.5		2.7	108.5		2.7

Content Uniformity N=10 (CV) = 99.8% (1.0%) for Acetaminophen in Test Drug
Content Uniformity N=10 (CV) = 100.9% (0.7%) for Acetaminophen in Reference Drug
Content Uniformity N=10 (CV) = 99.1% (2.1%) for Oxycodone in Test Drug
Content Uniformity N=10 (CV) = 101.1 (1.5%) for Oxycodone in Reference Drug

The formulation of the test drug product is presented below:

Ingredient	Amount per Capsule of Test Product
Oxycodone Hydrochloride	5 mg
Acetaminophen (Fine Powder)	400 mg
Corn Starch	(b)4 - Confident
Providone	
Purified Water	
Acetaminophen (Dense Powder)	100 mg
Pregelatinized Starch	(b)4 - Confident
Magnesium Stearate	
Gelatin Capsule	
Total Weight	630 mg

* Not included in formula weight. (b)4 - Confidential Business

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Comments:

1. The dissolution method and tolerance specification are in accordance with those published in USP 23. The dissolution results are acceptable.

2. The test drug is in conventional dosage form and does not present bioequivalence problems. It also has met the proper *in vitro* dissolution standard that is acceptable to the specification

published in USP 23. Therefore, a waiver from the human *in vivo* bioequivalence testing requirements is granted.

Recommendation:

1. The Division of Bioequivalence agrees that the information submitted by Royce Laboratories, Inc. demonstrates that Acetaminophen/Oxycodone HCl Capsule, 500 mg/5 mg, falls under 21 CFR Section 320.22(c) of the Bioavailability/Bioequivalence Regulations. The waiver of in vivo bioequivalence study for the test product is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test capsule to be bioequivalent to Tylox capsule, 500 mg/5 mg, manufactured by McNeil Laboratories/RW Johnson Pharmaceutical.

2. The dissolution testing conducted by Royce Laboratories, Inc. on its Acetaminophen/Oxycodone HCl Capsule, 500 mg/5 mg, Lot #NC-1302, is acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of 0.1 N hydrochloric acid at 37° C using USP 23 apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:

   Not less than [redacted] the labeled amounts of both acetaminophen and oxycodone are dissolved in 45 minutes.

/S/ 5/1/97

Lin-Whei Chuang
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG

/S/ 5/1/97

/S/

Concur Date: 5/6/97

for Nicholas Fleischer, Ph.D.
Director, Division of Bioequivalence

cc: ANDA 40234 (original, duplicate), Chuang, HFD-652, (Y.C. Huang), Drug File, Division File.

First Draft, LWC, 05/01/97, c:\wpfiles\40234w.d96
Final Pink, LWC, 05/01/97, x:\new\firmsnz\royce\ltrs&rev\40234.d96